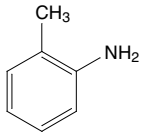
o-Toluidine and Its Hydrochloride

CAS Nos. 95-53-4 and 636-21-5

Reasonably anticipated to be human carcinogens

o-Toluidine was first listed in the *Third Annual Report on Carcinogens* (1983)

o-Toluidine hydrochloride was first listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

o-Toluidine and *o*-toluidine hydrochloride are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to *o*-toluidine hydrochloride caused tumors at several different tissue sites in rats and mice. In rats, it caused cancer of the connective tissue (several types of sarcoma) in the spleen and other organs in both sexes; benign and malignant tumors of the urinary bladder (transitional-cell papilloma and carcinoma) and mammary gland (adenoma and fibroadenoma) in females; and mesothelioma of the abdominal cavity and the scrotum and benign and malignant tumors of the subcutaneous tissue (mainly fibroma) in males. In mice, it caused blood-vessel tumors (hemangioma and hemangiosarcoma) in both sexes and benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in females (IARC 1982).

Cancer Studies in Humans

The human cancer studies available when *o*-toluidine was evaluated for listing in the *Third Annual Report on Carcinogens* were primarily case reports of urinary-bladder cancer occurring among workers exposed to dyes in addition to *o*-toluidine. These studies were inadequate for evaluating effects specifically from exposure to *o*-toluidine (IARC 1978, 1982). Since then, additional studies in humans have been identified. The International Agency for Research on Cancer classified *o*-toluidine as carcinogenic to humans based on cohort studies of workers exposed to *o*-toluidine that reported increased risk of urinary-bladder cancer (Baan *et al.* 2008).

Properties

o-Toluidine is an aromatic amine that exists at room temperature as a light-yellow liquid that darkens to reddish brown upon exposure to air (IPCS 1998, Akron 2009). It has an aromatic aniline-type odor. *o*-Toluidine is slightly soluble in water, soluble in alcohol, ether, and dilute acids, and miscible in carbon tetrachloride (HSDB 2009). *o*-Toluidine hydrochloride is the hydrochloride salt of this aromatic amine. It is a green or white crystalline solid at room temperature (Akron 2009). It is very soluble in water, soluble in alcohol, and insoluble in ether and benzene (HSDB 2009). It is sensitive to exposure to moisture and light (IARC 2000). Physical and chemical properties of *o*-toluidine and its hydrochloride are listed in the following table.

Property	*o*-Toluidine	*o*-Toluidine hydrochloride
Molecular weight	107.2[a]	143.6[a]
Specific gravity	1.008 at 20°C[a]	NR
Melting point	–16.3°C[a]	215°C[a]
Boiling point	200.3°C[a]	242.2°C[a]
Log K_{ow}	1.32[a]	1.62[b]
Water solubility	16.6 g/L at 25°C[a]	8290 mg/L at 25°C[b]
Vapor pressure	0.260 mm Hg at 25°C[b]	0.293 mm Hg at 25°C[b]
Vapor density relative to air	3.69[a]	NR
Dissociation constant (pK_a)	4.44 at 25°C[a]	4.39 at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009. NR = not reported.

Use

o-Toluidine and *o*-toluidine hydrochloride are used primarily as intermediates in the manufacture of more than 90 dyes and pigments (NCI 1979, IARC 1982, 2000). They are used in acid-fast dyestuffs, azo pigments and dyes, triarylmethane dyes, sulfur dyes, and indigo compounds and as a photographic dye. *o*-Toluidine is also used as an intermediate for synthetic rubber and rubber vulcanizing chemicals, pharmaceuticals, and pesticides and as a curing agent in epoxy resin systems. Other minor uses of *o*-toluidine and its hydrochloride salt are as an intermediate in organic synthesis and as an ingredient in a clinical laboratory reagent for glucose and hemoglobin analyses.

Production

In the United States, commercial production was first reported for *o*-toluidine in 1956 and for *o*-toluidine hydrochloride in 1922 (IARC 1982, 2000). Annual production of *o*-toluidine was estimated at 500,000 kilograms to 5 million kilograms (1.1 million to 11 million pounds) in the late 1970s, increasing to 6.6 million to 12.8 million kilograms (14.5 million to 28.2 million pounds) by the early 1990s (IARC 2000). In 2009, *o*-toluidine was manufactured by 18 companies worldwide, including 3 in the United States (SRI 2009), and was available from 18 U.S. suppliers (ChemSources 2009). *o*-Toluidine hydrochloride has not been commercially produced in the United States since 1975 (HSDB 2009); however, it was available from six U.S. suppliers in 2009 (ChemSources 2009). In 2008, U.S. imports of "toluidines and their derivatives, salts thereof" and "other toluidines and their derivatives, and salts thereof" totaled 33.8 million pounds (USITC 2009). No import volumes were reported for this category before 2003. U.S. exports for this category have been reported for every year since 1989; volumes ranged from a high of 21.6 million pounds in 1992 to a low of 3.9 million pounds in 2002. Reports filed from 1986 through 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *o*-toluidine totaled 10 million to 50 million pounds (EPA 2004).

Exposure

The potential routes of exposure to *o*-toluidine and its hydrochloride salt are inhalation, dermal contact, and ingestion (HSDB 2009). *o*-Toluidine is a metabolite of prilocaine, a topical anesthetic. The general population may be exposed to low concentrations of *o*-toluidine in indoor and outdoor ambient air, tobacco smoke, or food, or by dermal contact with commercial products. Consumers may possibly be exposed to *o*-toluidine from residues present in commercial dyes used on textiles (IARC 2000). *o*-Toluidine has been detected in blood and breast milk (Gazarian *et al.* 1995) and was measured in the urine of individuals with no known exposure at a median concentration of 0.12 µg/L (Weiss and Angerer 2002). *o*-Toluidine is present in cigarette smoke at a concentration of up to 144 ng per cigarette (Stabbert *et al.* 2003). It has been measured in the urine of smokers at a mean

concentration of 117 ng/L and in the urine of nonsmokers at 55 ng/L (Riedel *et al.* 2006). Hemoglobin (Hb) adducts of *o*-toluidine were measured in children at three locations in Germany who were either exposed or not exposed to environmental tobacco smoke (Richter *et al.* 2001). The first two locations were urban, and all children showed high levels of *o*-toluidine adducts, with no significant differences between the exposed and unexposed groups (Munich: 642 pg/g of Hb exposed, 620 pg/g unexposed; Augsburg: 574 pg/g exposed, 621 pg/g unexposed). At the third location, which was rural, all children had much lower levels of *o*-toluidine adducts, and levels differed significantly between the exposed and unexposed groups (376 pg/g of Hb exposed, 558 pg/g unexposed).

According to EPA's Toxics Release Inventory, environmental releases of *o*-toluidine between 1988 and 2009 ranged from 10,800 to 55,000 lb, while releases of *o*-toluidine hydrochloride ranged from 0 to 265 lb. In 2007, 16,348 lb of *o*-toluidine was released from 12 facilities, and 10 lb of *o*-toluidine hydrochloride was released from one facility (TRI 2009). *o*-Toluidine has been detected in effluents from refineries and production facilities and in river water, process water, and groundwater (IARC 2000). In 1979, it was measured in the Rhine River at concentrations of 0.03 to 1.8 µg/L and in Japan at concentrations of up to 20 µg/L (IPCS 1998).

Occupational exposure to *o*-toluidine or *o*-toluidine hydrochloride is most likely to occur through inhalation and dermal contact (Korinth *et al.* 2006). *o*-Toluidine has been measured in personal air samples and urine from automobile workers involved in rubber vulcanization, at concentrations ranging from 26.63 to 93.93 µg/m^3 in air and 54.65 to 242.88 µg/L in urine. The higher urine concentrations were measured in workers with impaired skin (Korinth *et al.* 2007). In another study of these workers, workplace ambient air concentrations of *o*-toluidine were 11.0 µg/m^3 for smokers and 61.4 µg/m^3 for nonsmokers, and urine concentrations were 14.5 µg/L for smokers and 38.6 µg/L for nonsmokers. It also appeared that skin-barrier creams recommended for use on the hands of workers had a negative effect, increasing the transfer of *o*-toluidine across the skin barrier. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 30,000 workers, including 15,500 women, potentially were exposed to *o*-toluidine. The potential for exposure was greatest among dye and pigment makers (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of *o*-toluidine on ships and barges.

Department of Transportation (DOT)

Toluidines are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: o-Toluidine is listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for *o*-toluidine and *o*-toluidine hydrochloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: o-Toluidine is a listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of *o*-toluidine or *o*-toluidine hydrochloride = U222, U328, K112, K113, K114.

Listed as hazardous constituents of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 5 ppm (22 mg/m^3) for *o*-toluidine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm for *o*-toluidine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm for *o*-toluidine.

o-Toluidine is listed as a potential occupational carcinogen.

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